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Authors: Dorota Gryko, Maksymilian Karczeski, and Michał Ociepa

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Cobalamin-catalysed chemical reactions – probing the role of nucleotide loop

Maksymilian Karczewski,[a] Michał Ociepa,[a] and Dorota Gryko*[a]

Abstract: The nucleotide loop in the vitamin B_{12} structure affects its biological and physicochemical properties, but its role in cobalamin-catalysed reactions still remains disputable. Herein, we show the synthesis of a series of model compounds including *N*-methylcobalamin (NMICbl) in a *base-off* form with the nucleotide attached. The structure-activity relationship studies reveal that in the studied cobalamin-catalysed reaction, the reduction step is not a rate-determining.

Introduction

Fine tuning of ligands' properties is a challenging task in the field of organometallic catalysis and changing their electronic and steric features are often required to achieve a suitable balance between the stability and reactivity of a catalyst.[1] Vitamin B_{12} (**1**, cobalamin), one of the most intriguing catalysts provided by Nature itself, is a Co-complex with highly functionalised corrin ring as an equatorial ligand and two distinct axial ligands (Figure 1). In mammalian cells it plays an important role of a cofactor in processes such as methylmalonyl-coenzyme A (CoA) rearrangements,[2] or methyl transfer reactions.[3] The catalytic activity of vitamin B_{12}, relying mainly on the redox chemistry of the central cobalt atom, enables successful application of this compound in synthetically useful reactions: dehalogenation, ring expansion, C-H activation, cyclopropanation.[4-7] However, due to its structural complexity, cobalamin is rarely perceived as a catalyst which catalytic efficacy can be improved via structure modifications. Although this may seem a challenging task, we believe that knowing the structure-activity relationship for cobalamin derivatives is essential for better understanding of their catalytic properties. One of the most characteristic structural features of native vitamin B_{12} is the so-called "nucleotide loop", located at the α face of the corrin ring with 5',6'-dimethylbenzimidazol (DMB) moiety as an α-axial ligand. The importance of the loop corroborates itself in the methylmalonyl-coenzyme A (CoA) rearrangement. Halpern and co-workers showed that in these reactions switching between base-on and base-off forms of the cofactor changes the strength of the Co-C bond enabling cobalamin to play a role of a "reversible free radical carrier".[8] The process is initiated by the homolytic dissociation of 5'-deoxyadenosyl-cobalt bond with the estimated energy of 109 kJ·mol^{-1} and proceeds via a radical mechanism. Furthermore, it has been reported that with an

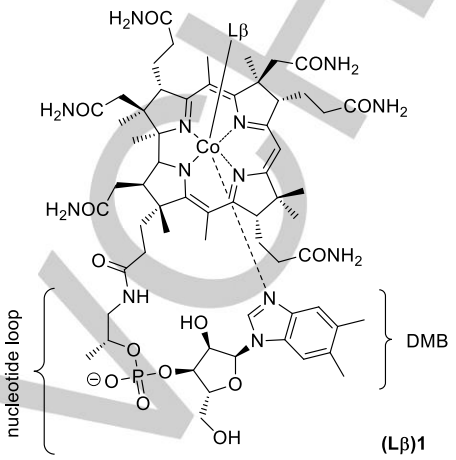

Figure 1. Structure of vitamin B_{12} (1, cobalamin).

increasing basicity of an α-axial ligand, the energy required to break the Co-C bond increases.[9] The *trans*-effect of the DMB ligand on the Co-β-ligand bond length was confirmed by X-ray analysis of various cobaloximes and vitamin B_{12} derivatives.[10,11] In this line, Zelder studied a model complex with imidazole as the α-axial ligand and showed that deprotonation of the nitrogen atom stabilizes the Co ion on the +3 oxidation state.[12] Réthey prepared compounds possessing 4-methylphenol in place of the heterocycle - DMB.[13] This artificial coenzyme proves not only to catalyse the metylmalonyl-CoA rearrangement, but also to have higher affinity towards methylmalonyl-CoA mutase itself. Cobinamide – a Cbl derivative lacking DMB, ribose and phosphate units – was as well used to study the $AdCH_2$-Co binding.[14-19]

Finke et al. focused on the radical chemistry behind the cleavage of the Co-C bond and found that the DMB base-on form favours Co-C homolysis over heterolysis. Though the presence of the nucleotide loop is not absolutely necessary for the Co-C homolytic step, it plays an essential role in preventing the radical intermediates from undergoing side reactions.[16] Our previous results suggest that the loop plays a vital role in reactions catalysed by Co(I) vitamin B_{12}.[7] The catalytic activity of an amphiphilic derivative of cobalamin – cobalester (Cble) was compared to that of cobinamide and heptamethyl cobyrinates (Cby) lacking the nucleotide loop, in a dimerization of benzyl bromide.[7] In this case, Cble proves superior to Cbi, however the lack of the loop in Cbi and Cby derivatives makes them imperfect models for base-off form of vitamin B_{12}, as they do not entirely reflect steric effects of the loop in natural cobalamin. Therefore, we believe that the question *'if the nucleotide loop provided to the vitamin B_{12} by Nature grants it superior catalytic properties'* can only be answered by comparing native vitamin B_{12} to model compounds (**4**-**6**) bearing all structural elements of cobalamin, but being either permanently locked in the *base-off* form (**6**) or possessing axial

[a] M. Karczewski, M. Ociepa, D. Gryko
Institute of Organic Chemistry, Polish Academy of Sciences
Kasprzaka 44/52
01-224 Warsaw, Poland
E-mail: dorota.gryko@icho.edu.pl
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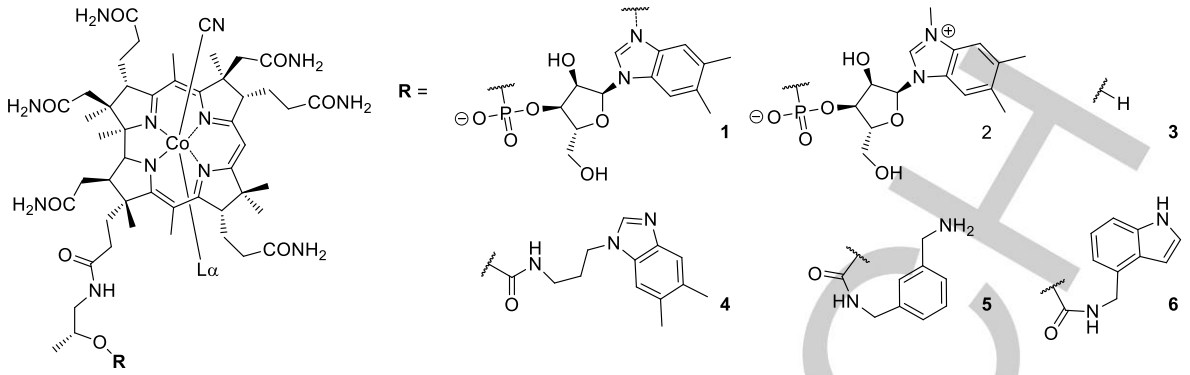
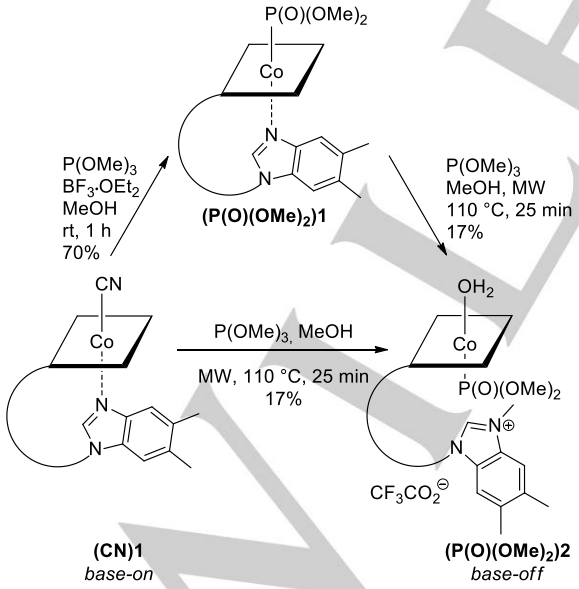


Figure 1 Comparison of structural features of our model compounds..

ligands and three cobinamide derivatives with different moieties at the hydroxyl group (**4-5**, Figure 2). Consequently, the effects of those changes were examined in the reductive dimerization of 1,1-diphenylethylene.

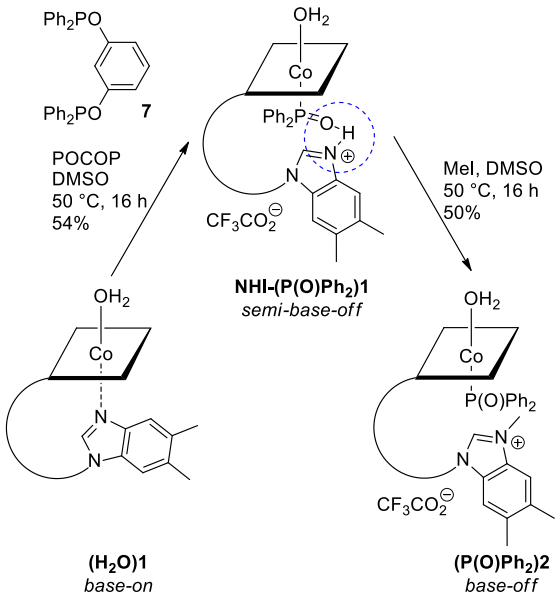
Results and Discussion

Synthesis of *N*-methylated cobalamins (2). To the best of our knowledge the only stable *base-off* form of cobalamin was obtained by Friedrich and Bernhauer in 1956 by methylating the nitrogen atom of the DMB moiety, then the methodology was further explored by Zelder.[20,21] However, previously published procedures were not suitable for the synthesis on a preparative scale, consequently we devised a new method of quaternization of DMB nitrogen atom by employing trimethylphosphite along with microwave irradiation (Scheme 1).



Scheme 1. Synthesis of **(P(O)(OMe)$_2$)2** directly from **(CN)1** or via **(P(O)(OMe)$_2$)1**.

Trimethyl esters of phosphorus inorganic acids are known as methylating agents for nitrogen bases.[22,23] Intriguingly, the reported reaction of $P(OMe)_3$ with **(CN)1** at room temperature leads only to the ligand exchange - from CN^- to $P(O)(OMe)_2^-$ giving red complex **(P(O)(OMe)$_2$)1** (Scheme 1). Its crystallographic structure clearly evidences longer Co-DMB bond (2.20 Å) in comparison to **(CN)1** (2.01 Å), thus more susceptible to chemical modifications.[24] However, when **(CN)1** and $P(OMe)_3$ were reacted in DMF at elevated temperature both the methylation of DMB moiety and the ligand exchange occurred (Scheme 1). Mild reaction temperature (45 °C) as well as the addition of Lewis acid ($BF_3{\cdot}OEt_2$) led only to complex **(P(O)(OMe)$_2$)1**, but reactions under microwave irradiation of either **(CN)1** or **(P(O)(OMe)$_2$)1** with $P(OMe)_3$ at 110 °C yielded a mixture of compounds with **(P(O)(OMe)$_2$)2** predominating. Other products, according to MS analysis, included derivatives bereft of the "nucleotide loop" – cobinamides (**3**) possessing various axial ligands. Subsequently, the reaction conditions were optimized and the desired compound **(P(O)(OMe)$_2$)2** was obtained in 17% yield. For reactions on 100 mg scale, the reaction time was prolonged to 40 min, to assure full conversion. An alternative methodology employed aquacobalamian (**(H_2O)1**) as a starting material (Scheme 2). Initially, complex **(H_2O)1** while reacted with reagent **7** formed a stable yellow complex of coblamin in a *semi-base-off* form, with the DMB moiety being protonated. The stability of this compound seems to arise from the intramolecular hydrogen bond formation with the α-ligand. The comparison of the experimental UV/Vis spectra of **NHI-(P(O)Ph$_2$)1** to the computed ones for four diastereoisomers differentiating in the side of a ligand attachment (α or β) and the atom coordinating to cobalt ion (phosphorus or oxygen) suggests the existence of this bond (Figure 3). Whereas binding of the phosphorous ligand on the β-face of macrocycle would result in a bathochromic shift (green and blue lines) in comparison to the native cobalamin, a hypsochromic shift was observed (orange line). Additionally, the shape experimental spectrum resembles the computed one for the diastereoisomer with the Co-P bond at the site resembled (pink). Complex **NHI-(P(O)Ph$_2$)1** could be methylated with as little as 10 equivalents of methyl iodide (compared to more than 100 equiv. of $P(OMe)_3$ and $6x10^5$ of MeI as reported by Zelder),[21] offering an facile access to *base-off* complex **2**.



Scheme 2. Synthesis of **(P(O)Ph$_2$)2** directly from **(H$_2$O)1** via *semi-base-off* **NHI-(P(O)Ph$_2$)1.**

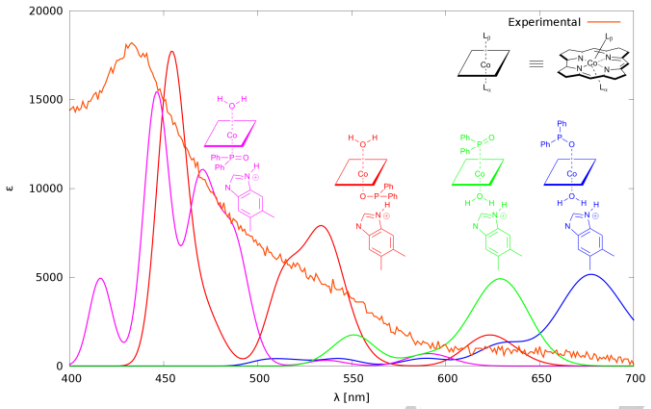
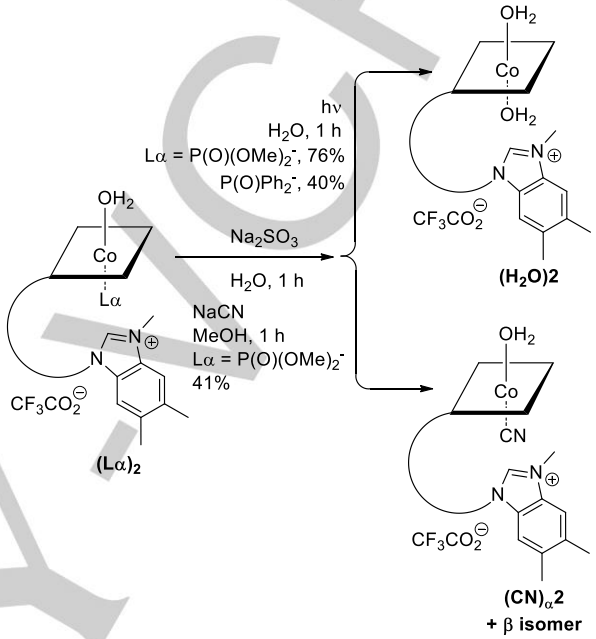


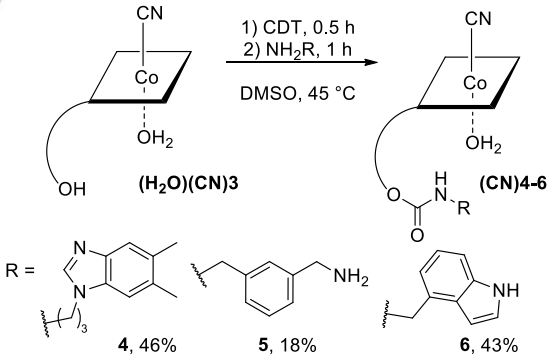
Figure 3. UV/Vis spectra for truncated structure of complex **NHI-(P(O)Ph$_2$)1** and four possible diastereoisomers (experimental (MeOH, C_M = 1.65 x 10^{-5} M) and computed (BP86/6-31G(d)/def2TZVP)

Anionic ligands are not desirable for the purpose of catalysis, as proved by Zhang et al.[25] and Zelder et al.,[26] hence the synthesized complex **2** was irradiated with light that led to products possessing molecule of water coordinated to the central atom. As the conversion was not quantitative, we addressed this issue by developing an efficient strategy for the replacement of the anionic ligands with a molecule of solvent (Scheme 3), which also proved to be a valuable tool for the quantitative transformation of **(CN)1** to **(H$_2$O)1** (See supporting information).

Synthesis of cobinamides with a "non-natural loop". Although performing reactions at the secondary, terminal OH group of cobinamide (**3**) was a challenging task, activation by CDT (1,1'-carbonyldi(1,2,4-triazole)) at elevated temperature and the subsequent reaction with primary amines allowed functionalisation of the macrocycle at the *f*-side chain (Scheme 4).



Scheme 3. Exchange of phosphate ligand to molecule of solvent or cyanide ligand.



Scheme 4. Modification of cobinamide (**3**) with amines.

Electrochemical behaviour of synthesised derivatives. The catalytic efficacy of cobalamin-type catalysts strongly depends on their redox properties. Therefore, we explored electrochemical characteristics of the *base-off* model compounds on the basis of a series of cyclic voltammograms (Table 1). The obtained results clearly shows that the coordination of the cobalt ion by DMB moiety decreases susceptibility of the coordination centre to reduction, as shown by the negative shift in redox potentials values for the

corresponding compounds in *base-on* forms (compare entries 2 with 5, 6 and 1with 4).

Base-off compounds **(H_2O)2**, **(CN)2** and **($P(O)(OMe)_2$)2** show similar E_{pc} values to that of cobinamide (**3**), indicating that the cobalt centre does not experience significant electronic effects from the presence of the blocked nucleotide loop. Diaqua complex **(H_2O)2** with two labile ligands undergoes reduction via analogous mechanism to that of aquacobalamin (**1**) with well separated redox couples Co(III)/Co(II) and Co(II)/Co(I). Moreover, CV for compound **(CN)2** evidences the existence of an equilibrium between (CN)(H_2O)NMICbl and $(CN)_2$NMICbl which is distinct from the redox behaviour of cyanocobalamin (**2**) but similar to that of cobyrinic acid derivatives.

The reduction potential of compound **(CN)4** and native cobalamin **(CN)1** differ by 0.13 V although they both possess the same base - DMB, this suggests that not only the base itself affects the reduction potential, but also the structure of a linker connecting the base and the corrin, as reported by Zelder et al.[27]

Table 1. Reduction potentials for different cobalamin derivatives in MeOH (*vs.* Ag/AgCl)

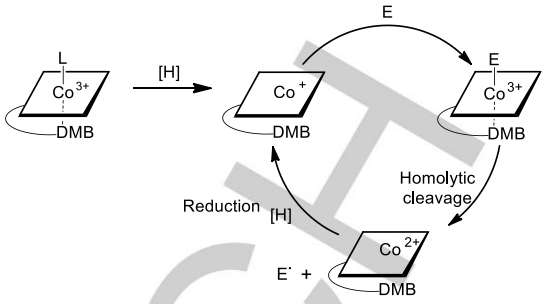
Entry	Catalyst	*base-off*	$E_{Pc}(Co^{III}\rightarrow Co^{II})$	$E_{Pc}(Co^{II}\rightarrow Co^{I})$
1	**(H_2O)1**	No	+0.10	-0.86
2	**(CN)1**	No	-1.01	-1.01
3	**($P(O)(OMe)_2$)1**	No	-1.03	-1.03
4	**(H_2O)2**	Yes	+0.25	-0.73
5	**(CN)2**	Yes	-0.49 (-1.24)[a]	-0.74 (-1.24)[a]
6	**($P(O)(OMe)_2$)2**	Yes	-0.77	-0.77
7	**(CN)4**	Yes	**-0.57**	-0.88
8	**(CN)5**	Yes	**-0.38**	-0.77
9	**(CN)6**	Yes	**-0.56**	-0.73
10	**(CN)(H_2O)3**	Yes	-0.51 (-1.20)[a]	-0.73 (-1.20)[a]

[a] Peaks corresponding to reduction of dicyano form.

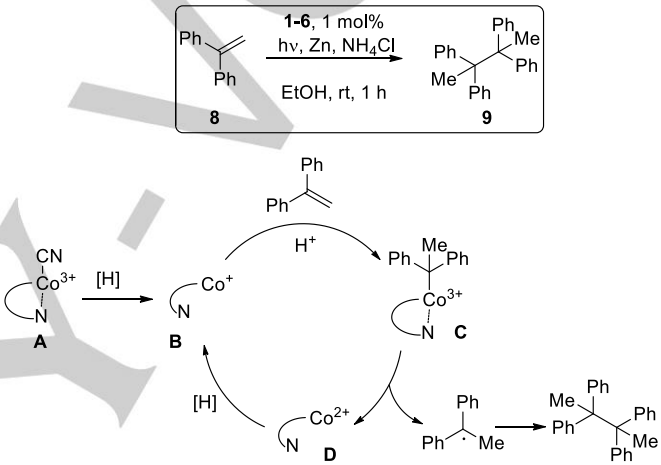
Catalytic activity studies

In a typical cobalamin-catalysed reaction, the most important steps featuring Cbl are its reduction to the Co(I) form and homolytic cleavage of the Co-C bond, which can undergo via photolytic or thermolytic pathway (Scheme 5).

Due to the fact that all studied compounds are polar, model reaction had to be performed in a highly polar solvent in order to exclude any solubility issues. Therefore, we examined the synthesised set of cobalt catalysts in a reductive dimerization 1,1-diphenylethylene (Scheme 6), which could be performed in EtOH, as reported by van der Donk et. al.[28,29] Mechanistic studies of cobalamin-catalysed reactions of alkenes (including styrene derivatives)[29,30] proves that the active form of the catalyst is its Co(I) form **B** and is likely to proceed via the formation of Co-C complex **C** (Scheme 6).



Scheme 5. Typical catalytic cycle of the cobalamin-catalysed radical reactions (E – electrophile).



Scheme 6. Model reaction chosen for comparison of cobalamin-like catalysts - reductive dimerization of 1,1-diphenylethylene (**8**) and a plausible mechanism proposed by van der Donk.[29]

The dimerization was affected by the presence of the nucleotide loop, but not its basicity, contrary to the phenomena of well-studied *trans*-effect. The highest yield was obtained when native cobalamian (**1**) served as a catalyst for the discussed reaction in either the cyano or aqua form, (Table 2, entries 1, 2). However once the "loop" was unable of donating the lone electron pair to the central atom, the yield decreased (entry 3, 4). Both derivatives **(H_2O)1** and **(CN)1** are in *base-on* form and though they have different electrochemical behaviour as depicted by cyclic voltammetry, they yielded almost the same quantity of products (entry 1, 2). This result indicates that in the studied reaction, the reduction step is not a rate-determining. Moreover, green colour of the reaction mixture (characteristic for Co(I) form of cobalamins), indicates that the complex **B** is a steady-state of a catalyst during the reaction (see SI).

Interestingly, when the reaction was extended to 24 h, there was little to no change in the yield for native cobalamin (**1**, entry 1 in parentheses) in contrast to catalyst **3** (entry 4 in parentheses) for which the yield increased to 99%, suggesting that with an increased rate of the dimerization, side products started forming (see SI). The cobinamide derivative **5** with a

primary amine serving as the axial ligand, was the least efficient catalyst, presumably due to presence of the -NH_2 group (entry 7).

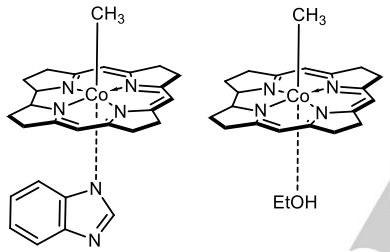
Table 2. Yields of dimer **9** obtained in model reaction.

Entry	Catalyst	*base-off*	Yield [%]
1	**(CN)1**	No	80 (78)[a]
2	**(H_2O)1**	No	77
3	**(H_2O)2**	Yes	65
4	**(CN)(H_2O)3**	Yes	68 (99)[a]
5	**(CN)6**	Yes	74
6	**(CN)4**	Yes	75
7	**(CN)5**	Yes	8

[a] Yield after 24 h;

DFT calculations

In order to determine how binding of a loop influences the Co-C bond strength in the plausible intermediate **C** (Scheme 6), we performed calculations of the Co-C bond dissociation energy using the method BP86/TZVP and truncated structures of *base-on* and *base-off* forms of cobalamin (Scheme 7) proposed by Kozlowski et al.[9]



Base-on **Base-off**

Scheme 7. Truncated structures of *base-on* and *base-off* forms of vitamin B_{12} used in calculations.

In the case of *base-off* form EtOH was chosen as an *α*-axial ligand as our model reaction was performed in this solvent. The results of DFT calculations confirmed that the coordination by the nucleotide ligand leads to the formation of more stable Co-C complex. Substitution of DMB with EtOH significantly increases the distance between *α*-ligand and the central cobalt atom, while the *trans*-effect manifests itself in a decrease of the bond dissociation energy of Co-C bond by 75 kJ/mol (Table 3).

Table 3. Calculated bond dissociation energies and bond lengths for model catalysts.

Entry	*α*-ligand	Co-C_β/ Å	Co-*α* ligand/ Å	$E_{Co\text{-}C}$/ kJ·mol^{-1}
1	DMB	1.976	2.235	170.3
2	EtOH	1.977	2.473	95.0

As a consequence, the binding of the loop to the cobalt ion facilitates formation of the Co-C bond. Moreover, they point to the possible dependence of catalytic properties on the nucleotide ligand.

Conclusions

In conclusion, new *N*-methylated cobalamins **2** with four different axial ligands – CN^-, $P(O)(OMe)_2^-$, $P(O)Ph_2^-$ and H_2O, were synthesised by two different methods - a) microwave irradiation of methanol solution of $P(OMe)_3$ and cyanocobalamin (**(CN)1**), b) by the formation of the *semi-base-off* form and the subsequent methylation with methyl iodide. Three different models - cobinamide derivatives (**4-6**), with an extended *f*-side chain were obtained.

Catalytic activity of cobalt catalysts were tested in the model reductive dimerization of 1,1-diphenylethylene (**8**). The data obtained in catalytic experiments suggests that in dimerization, complexation of the cobalt ion plays a vital role, influencing the reaction yield. The *base-on* derivatives proved to react with alkene **8** with higher rate, however more controlled reaction with *base-off* derivatives allowed to obtain exclusively dimerization product **9** without the formation of side products. The results obtained for reactions catalyzed by compounds **2**, **4**, **6** suggest that the sole presence of the nucleotide loop in the structure of a catalyst has an impact on their catalytic property and the outcome of the reaction.

Our findings provide new insights into properties of *base-off* form of vitamin B_{12}. We expect that the greater understanding of the influence of the nucleotide loop on catalytic properties of vitamin B_{12} and its derivatives will soon result in a development of new cobalamin catalysed reactions of general use.

Experimental Section

General information

Commercially available reagents and solvents were used as received. 1H and 13C NMR spectra were recorded at room temperature on a Bruker or Varian 500 MHz spectrometer with the residual solvent peak as an internal standard. Data are reported as follows: chemical shift, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and the number of protons. UV-visible spectra were recorded on a Jenway 7315 spectrophotometer. High resolution ESI mass spectra were recorded on a Mariner and SYNAPT spectrometer. All the reactions and products purities were monitored using RP HPLC technique. Preparative chromatography was performed using Knauer RP C-18 column, 250x20 mm, with flow rate of 9 ml min^{-1} with water purified by reverse osmosis and HPLC grade MeCN or MeOH as eluents. HPLC analytical measurement conditions: column, Kromasil Eternity-5-C18, 250 mm × 4.6 mm with a precolumn; UV/vis detection, temperature, 30 °C; wavelengths 254 nm and 361 nm, flow rates 1 ml min^{-1}. Compounds **3** and **7** were synthesised according to the literature procedures.[31,32] Calculations were performed using Gaussian 09 E.01, using BP86 method with 6-31G(d) basis set for C,H,N,O and def2TZVP for cobalt.[33]

Analytical chromatography gradient

Program 1

Entry	H_2O (0.5‰ TFA) [%]	MeCN [%]	Time [min]
1	99	1	0
2	85	15	5
3	20	80	30
4	99	1	35

Program 2

Entry	H_2O (0.5‰ TFA) [%]	MeCN [%]	Time [min]
1	90	10	0
2	30	70	15

Preparative chromatography gradient

Entry	H_2O (0.5‰ TFA) [%]	MeOH [%]	Time [min]
1	99	1	0
2	57	43	60
3	50	50	70
4	99	1	75

General work up procedure prior to RP chromatography

All reactions requiring HPLC (RP) purification were diluted with 10-fold excess of Et_2O and poured on a pad of celite. The solid residue was washed twice with 2-fold excess of Et_2O, and flushed with MeOH. Solvents were evaporated and the residue was dissolved in a minimal amount of MeOH, transferred to 50 mL falcon tube, diluted with Et_2O and centrifuged. Resulting solid was washed with Et_2O, *n*-pentane and dried *in vacuo*.

General procedure for the synthesis of aqua complexes

To remove the cyanide ligand from cobalamin and its derivatives, a sample of cyano complex (22 µmol) was dissolved in H_2O (50 mL) and Na_2SO_3 (0.5 g, 3.9 mmol) was added. The resulting mixture was stirred for 1 hour. Than it was diluted with H_2O (100 mL) and solvents were removed under reduced pressure. The resulting crude was redissolved in EtOH and filtered through a pad of celite. Again solvent was removed under reduced pressure; the resulting solid was dissolved in H_2O (22 mL) and irradiated with visible light (LED, 300 lm, warm). Thereafter solvent was evaporated and the crude was purified by chromatography.

General procedure for CDT coupling

(CN)(H_2O)3 (30 mg, 27 µmol) and CDT (80 mg, 487 µmol) were placed in a tube with a Teflon screw and flushed with argon prior to addition of dry NMP (1 mL). The reaction was put in a preheated oil bath for 50 °C, for 30 min. Afterwards an amine (600 µmol) was added in a stream of argon and the resulting mixture was heated for another hour. The crude mixture was purified by column chromatography.

General procedure for reductive dimerization of 8

Freshly activated zinc dust (98 mg, 1.5 mmol), NH_4Cl (45 mg, 1.7 mmol), a catalyst (2.5 µmol) and EtOH (2.5 mL) were placed in a test tube and sealed with septum. The reaction was degassed using ultrasounds with argon being passed through the reaction mixture. Once the colour change was observed, 1,1-diphenylethylene (**8**, 45 µL, 0.25 mmol) was added via septum. The reaction was irradiated with visible light (LED, 300 lm, warm) with vigorous stirring to assure good zinc dispersion and for either 1 hour or 24 hours. The crude reaction mixture was diluted with Et_2O (20 mL) and filtered through a pad of celite. The resulting filtrate was concentrated under reduced pressure and purified by flash chromatography using hexanes:AcOEt mixture (97:3) as an eluent. Appropriate fractions were collected, solvents removed under reduced pressure and the resulting white solid was dried *in vacuo*.

Cyclic voltammetry

A cylindrical three-electrode cell was equipped with a glassy carbon working electrode, a 25 mm platinum wire as the counter electrode and an Ag/AgCl (3.0 M NaCl) electrode as the reference electrode. The scan rate for a typical experiment was 100 $mV{\cdot}s^{-1}$. The solution of the vitamin B_{12} derivative (2.0×10^{-3} M) and n-$Bu_4N^+ClO_4^-$ (1.0×10^{-1} M) in dry MeOH was deaerated by Ar gas bubbling before the measurements, and the cyclic voltammetry was carried out under an Ar gas atmosphere at room temperature. The E1/2 value of the ferrocene–ferrocenium (Fc/Fc^+) in MeOH was +0.44 V vs. Ag/AgCl with this setup.

Compound ($P(O)(OMe)_2$)2

Synthesis from (CN)1 Cyanocobalamin (92 mg, 68 µmol) was evenly distributed among seven microwave vessels equipped with stirring bars. The substrate was dissolved in a mixture of MeOH (0.6 mL) and $P(OMe)_3$ (0.1 mL, 0.8 mmol). Each vessel was irradiated with microwaves at 110 °C for 25 min. After workup and HPLC (RP) 20 mg (17%, 13 µmol) of yellow-brown solid was obtained.

Synthesis from ($P(OMe)_2$)1 Substrate (30 mg, 21 µmol) was dissolved in a mixture of MeOH (1.8 mL) and $P(OMe)_3$ (0.15 mL, 1.2 mmol). The reaction was irradiated with microwaves maintaining temperature of 110 °C for 10 min. After workup and HPLC (RP) 5 mg (17%, 3 µmol) of yellow-brown solid was obtained.

^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.59 (s, 1H), 7.99 (t, *J* = 4.8 Hz, 1H), 7.74(d, *J* = 10.8 Hz, 2H), 7.67 (d, *J* = 14.4 Hz, 2H), 7.56 (s, 1H), 7.49 (s, 1H), 7.39(s, 1H), 7.32 (s, 1H), 7.24 (s, 1H), 7.06 (s, 1H), 6.96 (s, 1H), 6.81 (s, 2H), 6.73 (s,1H), 6.71 (s, 1H), 6.50 (d, *J* = 4.2 Hz, 1H), 4.89 (d, *J* = 5.8 Hz, 1H), 4.63 - 4.57(m, 1H), 4.57 - 4.51 (m, 2H), 4.50 (d, *J* = 9.0 Hz, 1H), 4.32 (d, *J* = 10.6 Hz, 1H), 4.40 (d, *J* = 2.9 Hz, 1H), 4.15 (quint, *J* = 6.1 Hz, 1H), 4.08 - 4.00 (m, 1H), 4.02(s, 3H), 3.58 (td, J1 = 3.73 Hz, J2 = 12.0 Hz, 3H), 3.34 (d, *J* = 3.0 Hz, 2H), 3.25(d, *J* = 10.9 Hz, 1H), 3.10 (d, *J* = 10.9 Hz, 3H), 3.16 - 3.02 (m, 2H), 3.00 - 2.94 (m, 1H), 2.97 (d, *J* = 11.0 Hz, 3H), 2.86 (s, 1H), 2.61 (d, *J* = 1.8 Hz, 1H), 2.59 (s, 1H), 2.55 (s, 1H), 2.52 (dd, J_1 = 2.2 Hz, J_2 = 4.1, 1H), 2.40 (d, *J* = 14.2 Hz, 5H), 2.33 (s, 3H), 2.31 (s, 1H), 2.30 (s, 3H), 2.21 (d, *J* = 8.2 Hz, 2H), 2.26 - 2.16 (m, 1H), 2.11 - 2.03 (m, 1H), 2.02 - 1.91 (m, 3H), 1.91 - 1.72 (m, 4H), 1.67 (s, 3H), 1.55 (s, 3H), 1.59 -1.47 (m, 1H), 1.43 (d, *J* = 8.1 Hz, 1H), 1.31 (s, 5H), 1.28 - 1.13 (m, 2H), 1.06 (d, *J* = 6.3 Hz, 2H), 1.04 (s, 2H), 0.99 (s, 2H), 0.86 (t, *J* = 7.2 Hz, 1H), 0.80 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (DMSO-d6, 150 MHz) δ 177.3, 175.7, 174.7, 174.2, 173.9, 173.5, 173.3, 173.2, 173.2, 172.9, 171.4, 163.7, 163.3, 157.9, 157.7, 140.7, 135.9, 135.8, 130.1, 129.2, 114.1, 112.8, 107.7, 106.0, 97.2, 87.8, 86.6, 86.5, 85.7, 75.0, 74.1, 72.1, 70.0, 61.0, 54.3, 54.2, 53.7 (d, *J* = 42 Hz), 53.4 (d, *J* =

36 Hz), 52.5, 49.9, 46.7, 45.6, 45.2, 41.7, 41.2, 38.7, 35.3, 33.2, 32.9, 32.5, 32.2, 30.7, 27.5, 26.4, 25.7, 23.8, 20.1, 20.0, 19.4, 19.0, 17.3, 16.6, 15.71, 15.70, 15.2. ^{31}P NMR (DMSO-d_6, 288 MHz) δ 34.1, 0.1. HRMS (ESI-TOF) *m/z* calcd for $C_{65}H_{97}CoN_{13}O_{17}P_2Co$ $[M\text{-}CF_3CO_2]^+$: 1452.5933, found 1452.5894. IR (KBr, cm^{-1}): 3376, 3196, 2976, 2947, 1667, 1621, 1573, 1496, 1452, 1406, 1350, 1221, 1205, 1153, 1118, 1069, 1029, 1002, 951, 884, 785, 731, 566. UV/vis (H_2O) λ_{max} (nm) (ε, M^{-1} cm^{-1}):219 (2.6×103), 258 (1.8×103), 279 (1.6×103), 318 (1.2×103), 345 (1.1×103), 401 (7.1×102), 437 (7.1×102). HPLC: $t_{analytical\ 1}$ = 16.2 min, $t_{preparative}$ = 15.32 min.

Compound (CN)2

(P(O)(OMe)$_2$)2 (40 mg, 26 µmol) was transformation to aqua complex according to the general procedure described above and the resulting crude was dissolved in MeOH (5 mL) and NaCN (6 mg) was added. The resulting mixture after work-up was purified by HPLC (RP) yielding 16 mg of red solid (41%, 11 µmol).

^{1}H NMR (CD_3OD, 500 MHz) δ 9.42 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.66 (d, *J* = 9.4 Hz, 1H), 6.55 (s, 1H), 6.50 (d, *J* = 5.4 Hz, 1H), 6.47 (t, *J* = 2.4 Hz, 1H), 4.71 (s, 1H), 4.50 (d, *J* = 9.2 Hz, 1H), 4.31 (d, *J* = 9.3 Hz, 2H), 4.11 (d, *J* = 4.3 Hz, 3H), 4.07 (d, *J* = 10.4 Hz, 1H), 3.89 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.78 (s, 2H), 3.71 (dd, *J* = 6.1, 4.9 Hz, 1H), 3.54 (s, 1H), 3.45 - 3.40 (m, 1H), 3.28 (d, *J* = 5.0 Hz, 1H), 3.25 - 3.11 (m, 1H), 2.78 (d, *J* = 14.1 Hz, 1H), 2.75 - 2.70 (m, *J* = 6.1 Hz, 1H), 2.65 (d, *J* = 14.0 Hz, 1H), 2.61 - 2.49 (m, 3H), 2.48 (s, 5H), 2.46 (d, *J* = 2.6 Hz, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.37 - 1.84 (m, 8H), 1.83 (s, 2H), 1.78 - 1.72 (m, 1H), 1.71 (s, 1H), 1.67 (s, 1H), 1.60 (s, 3H), 1.57 (d, *J* = 5.0 Hz, 2H), 1.39 (s, 2H), 1.37 (s, 3H), 1.34 (s, 1H), 1.32 - 1.23 (m, 3H), 1.21 (dd, *J* = 8.5, 6.4 Hz, 3H), 1.15 (s, 1H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (CD_3OD, 125 MHz) δ 180.4, 179.9, 179.7, 178.9, 178.7, 178.5, 177.5, 175.8, 175.6, 174.6, 165.9, 165.7, 165.3, 142.0, 132.0, 131.2, 114.9, 113.6, 108.3, 106.7, 96.1, 94.8, 89.1, 88.5, 87.0, 85.0, 76.8, 76.3, 73.8, 72.8, 62.8, 61.0, 60.4, 58.6, 57.7, 57.4, 57.0, 55.5, 55.3, 52.2, 46.7, 46.2, 43.9, 42.8, 40.7, 40.2, 36.4, 36.2, 35.3, 34.2, 33.9, 33.4, 33.2, 33.0, 31.7, 28.3, 28.1, 28.0, 27.6, 27.1, 26.8, 25.0, 23.4, 22.9, 21.8, 20.5, 20.3, 20.0, 19.8, 19.6, 18.0, 17.7, 17.39, 16.5, 16.4, 14.4. HRMS (ESI-TOF) *m/z* calcd for $C_{64}H_{91}CoN_{14}O_{14}PCo$ $[M]^+$ 1369.5909, found 1369.5900. IR (KBr, cm^{-1}): 3333, 3190, 2966, 2876, 2135, 1667, 1614, 1577, 1499, 1449, 1396, 1357, 1311, 1219, 1153, 1116, 1069, 993, 951, 845, 581. UV/vis (H_2O) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 221 (4.7×104), 277 (1.7×104), 354 (2.6×104), 498 (8.8×103), 525 (8.3×103). HPLC: $t_{analytical\ 1}$ = 14.70 and 15.00 min, $t_{preparative}$ = 57.9 and 63.2 min.

Compound (H_2O)2

(P(O)(OMe)$_2$)2 or **(P(O)Ph$_2$)2** (40 mg, 26 µmol) were transform into aqua complexes according to the general procedure described above and purified using HPLC (RP) yielding either 26 mg (76%, 20 µmol) or 13 mg (40%, 10 µmol) of red solid respectively.

^{1}H NMR (CD_3OD, 500 MHz) δ 9.45 (s, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 6.52 (s, 1H), 6.50 (s, 1H) 4.93 (s, 1H), 4.71 (s, 1H), 4.55 (s, 1H), 4.34 (t, *J* = 5.5 Hz, 1H), 4.11 (s, 3H), 3.80 (t, *J* = 3.5 Hz, 2H), 3.69 (d, *J* = 19 Hz, 1H), 3.43 (s, 3H), 3.21 (d, *J* = 12.5 Hz, 1H), 2.83 (s, 1H), 2.77 (s, 1H), 2.62 - 2.48 (m, 12H), 2.46 (s, 3H), 2.45 (s, 3H), 2.41 - 2.26 (m, 3H), 2.26 - 2.12 (m, 4H), 1.85 - 1.79 (m, 3H), 1.81 (s, 3H), 1.66 (s, 3H), 1.63 (s, 4H), 1.45 (d, *J* = 7.6 Hz, 3H), 1.32 (d, *J* = 6.3 Hz, 2H), 1.30 (d, *J* = 1.5 Hz, 1H), 1.28 (s, 3H), 1.26-1.23 (m, 1H), 1.20 (s, 1H), 1.192 (s, 1H), 1.188 (s, 1H), 1.17 (s, 2H), 1.16 (s, 1H), 0.89 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (CD_3OD, 125 MHz) δ 181.0, 180.9, 176.2, 174.7, 173.9, 173.6, 164.5, 164.3, 162.8, 140.6, 136.9, 130.6, 129.5, 113.4, 112.2, 104.9, 103.3, 92.8, 87.8, 87.2, 87.0, 84.8, 75.8, 75.0, 74.8, 72.3, 71.4, 65.5, 61.3, 59.4, 57.2, 56.9, 56.0, 55.5, 54.1, 49.8, 44.6, 42.1, 41.2, 39.6, 39.1, 35.2, 33.9, 32.9, 32.5, 32.2, 31.9, 30.1, 26.7, 25.8, 22.0, 21.1, 19.2, 19.1, 18.5, 18.3, 18.0, 17.1, 16.7, 16.1, 15.2, 14.0, 13.0. HRMS (ESI-TOF) *m/z* calcd for $C_{63}H_{91}CoN_{14}O_{14}PCo$ $[M]^+$ 1343.5878, found 1343.5874. IR (KBr, cm^{-1}): 3348, 3198, 2973, 2936, 2875, 1669, 1621, 1580, 1502, 1452, 1401, 1335, 1283, 1200, 1138, 1069, 993, 951, 886, 841, 801, 722, 584. UV/vis (H_2O) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 223 (3.5×104), 274 (1.7×104), 349 (1.8×104), 403 (3.2×103), 494 (7.3×103), 518 (7.6×103). HPLC: $t_{analytical\ 1}$ = 12.1 min, $t_{preparative}$ = 60.7 min.

Compound (P(O)(OMe$_2$)1[24]

(CN)1 (102 mg, 75 µmol) was dissolved in MeOH (6 mL) and $P(OMe)_3$ (0.25 mL, 2.1 mmol) followed up with addition of $BF_3{\cdot}OEt_2$ (0.25 mL, 2.mmol). After stirring for 1 hour the reaction was worked up as described above and purified using HPLC (RP) yielding 61 mg of red solid (57%, 43 µmol).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.71 (s, 1H), 7.65 (s, 1H), 7.57 (d, *J* = 22.1 Hz, 3H), 7.32 (s, 1H), 7.23 (s, 1H), 7.11 (s, 1H), 7.01 (d, *J* = 10.8 Hz, 2H), 6.89 (d, *J* = 6.4 Hz, 2H), 6.74 (s, 1H), 6.57 (s, 1H), 6.50 (s, 1H), 6.35 (s, 1H), 6.19 (s, 1H), 6.10 (s, 1H), 5.99 (s, 1H), 5.95 (s, 1H), 4.53 (d, *J* = 8.6 Hz, 1H), 4.49 (s, 1H), 4.12 (d, *J* = 6.6 Hz, 1H), 4.03 (d, *J* = 10.6 Hz, 1H), 3.92 (d, *J* = 3.9 Hz, 2H), 3.72 – 3.64 (m, 1H), 3.53 (d, *J* = 18.9 Hz, 3H), 3.22 (d, *J* = 10.4 Hz, 3H), 3.10 (d, *J* = 10.4 Hz, 4H), 2.74 (s, 1H), 2.64 (d, *J* = 11.6 Hz, 2H), 2.43 (s, 5H), 2.39 (s, 5H), 2.35 – 2.19 (m, 5H), 2.17 (s, 4H), 2.16 (s, 4H), 2.08 (d, *J* = 12.6 Hz, 1H), 2.06 – 1.92 (m, 2H), 1.85 (s, 1H), 1.75 (d, *J* = 12.6 Hz, 2H), 1.67 (s, 5H), 1.56 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H), 1.25 – 1.19 (m, 2H), 1.16 (s, 3H), 1.09 (t, *J* = 5.7 Hz, 1H), 1.05 (s, 3H), 0.84 (s, 1H), 0.30 (s, 3H). HRMS (ESI-TOF) *m/z* calcd for $C_{64}H_{94}CoN_{13}O_{17}P_2CoNa$ $[M+Na]^+$ 1460.5596 found 1460.5583. HPLC: $t_{analytical\ 1}$ = 13.95 min, $t_{preparative}$ = 14.2 min.

Compound NHI-(P(O)Ph$_2$)1

(H$_2$O)1 (50 mg, 36 µmol) was put in a vial and dissolved in DMSO (2 mL), followed by addition of compound **7** (117 mg, 420 µmol). The vial was kept in a heating mantel with temperature set for 50 ˚C for 16 hours. The crude was diluted with 2 ml of AcOEt and worked up as described above, followed by HPLC (RP) yielding 30 mg (54%, 20 µmol) yellow-brown solid.

^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.96 (s, 1H), 7.85 (s, 2H), 7.64 (d, *J* = 36.4 Hz, 5H), 7.56 (s, 2H), 7.41 (d, *J* = 20.6 Hz, 5H), 7.34 (s, 3H), 7.24 – 7.11 (m, 13H), 7.08 (t, *J* = 6.3 Hz, 4H), 6.90 (d, *J* = 22.6 Hz, 3H), 6.82 (s, 2H), 6.80 – 6.74 (m, 4H), 6.69 (s, 1H), 6.43 – 6.37 (m, 4H), 4.67 (d, *J* = 10.4 Hz, 2H), 4.65 (s, 1H), 4.61 (s, 1H), 4.58 (s, 1H), 4.44 (d, *J* = 9.8 Hz, 1H), 4.24 (t, 1H), 3.95 – 3.91 (m, 1H), 3.59 (s, 3H), 3.56 (d, *J* = 8.9 Hz, 2H), 3.23 (d, *J* = 13.2 Hz, 1H), 3.14 (s, 3H), 2.71 (s, 2H), 2.43 – 2.34 (m, 3H), 2.31 (s, 5H), 2.28 (s, 8H), 2.18 (d, *J* = 16.5 Hz, 6H), 2.17 – 2.06 (m, 12H), 2.04 – 1.88 (m, 10H), 1.83 (d, *J* = 9.3 Hz, 4H), 1.69 (dd, *J* = 32.3, 8.6 Hz, 6H), 1.63 (s, 6H), 1.51 (d, *J* = 7.1 Hz, 4H), 1.46 (d, *J* = 6.9 Hz, 9H), 1.31 – 1.25 (m, 2H), 1.22 (s, 5H), 1.13 – 1.07 (m, 6H), 0.86 (t, *J* = 7.2 Hz, 2H), 0.60 (d, *J* = 14.9 Hz, 4H), 0.44 (s, 4H), 0.16 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d6) δ 177.55, 176.18, 175.32, 175.07, 173.83, 173.60, 173.52, 173.44, 172.58, 171.35, 171.26, 165.37, 164.49, 163.66, 159.54, 157.66, 140.01, 136.42 (d, *J* = 53.7 Hz), 135.26 (d, *J* = 55.9 Hz), 133.38, 130.41, 129.87, 129.23, 128.85 (d, *J* = 5.3 Hz), 128.48 (d, *J* = 10.5 Hz), 127.88 (d, *J* = 11.1 Hz), 127.71 (d, *J* = 11.8 Hz), 118.65, 115.10, 112.58, 110.03, 108.21, 98.92, 87.30, 86.51, 85.66, 75.37, 74.33, 71.65, 71.07, 64.80, 60.94, 58.72, 54.22, 53.84, 51.88, 48.56, 46.24, 45.42, 44.45, 33.39, 32.44, 32.22, 32.10, 32.01, 31.71, 30.24, 27.19,

26.12, 25.82, 23.50, 21.62, 21.59, 20.03, 19.55, 19.09, 18.67, 17.46, 16.24, 15.55, 15.47, 15.06, 13.79. 31P NMR (243 MHz, DMSO-d6) δ 66.42, -1.30; HRMS (ESI-TOF) *m/z* calcd for $C_{74}H_{99}CoN_{13}O_{15}P_2Na$ $[M+Na+]^{2+}$ 776.8093 found 776.8040; UV/vis (MeOH) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 265 (2.5×104), 327 (2.0×104), 433 (1.1×104); HPLC: $_{tanalytical\ 1}$= 15.14 min, $t_{preparative}$ = 16.0 min.

Compound (P(O)Ph$_2$)2

(P(O)Ph$_2$)1 (20 mg, 16 µmol) was put in a vial and dissolved in DMSO (2 mL), followed by addition of MeI (15 µL, 160 µmol) The vial was kept in a heating mantel with temperature set for 50 ˚C for 16 hours. The crude was diluted with AcOEt (2 mL) and worked up as described above, followed by purification using HPLC (RP) yielding 10 mg (50%, 8 µmol) yellow-brown solid.

^{1}H NMR (500 MHz, CD_3OD) δ 9.41 (s, 1H), 7.72 – 7.62 (m, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.15 (dd, *J* = 7.4, 5.5 Hz, 3H), 6.86 (dd, *J* = 10.9, 8.2 Hz, 2H), 6.47 (t, *J* = 8.5 Hz, 2H), 4.78 – 4.72 (m, 1H), 4.67 (d, *J* = 4.1 Hz, 1H), 4.64 (s, 1H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.30 (t, 1H), 4.09 (s, *J* = 7.0 Hz, 2H), 4.07 – 4.02 (m, 1H), 3.85 (d, *J* = 4.9 Hz, 1H), 3.74 (t, 1H), 3.31 (dt, *J* = 3.2, 1.6 Hz, 3H), 3.26 (d, *J* = 4.9 Hz, 1H), 3.19 (d, *J* = 14.7 Hz, 1H), 2.88 (t, 1H), 2.62 (ddd, *J* = 24.4, 16.2, 10.5 Hz, 1H), 2.56 – 2.48 (m, *J* = 16.0, 6.3 Hz, 1H), 2.45 (d, *J* = 14.2 Hz, 6H), 2.40 (s, 3H), 2.35 (dd, *J* = 9.5, 4.3 Hz, 1H), 2.32 (s, 3H), 2.30 – 2.25 (m, 2H), 2.25 – 2.11 (m, 2H), 2.11 – 2.01 (m, 2H), 2.01 – 1.95 (m, 2H), 1.91 – 1.82 (m, 2H), 1.80 (s, 4H), 1.76 (d, *J* = 11.9 Hz, 1H), 1.67 – 1.63 (m, 1H), 1.62 (d, *J* = 4.5 Hz, 3H), 1.61 (s, 3H), 1.42 (t, 2H), 1.39 – 1.23 (m, 2H), 1.19 (s, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 1H), 0.73 (s, 3H), 0.65 (s, 3H), 0.36 (d, *J* = 14.3 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 178.04, 176.90, 176.55, 176.22, 175.96, 175.86, 174.95, 174.24, 173.39, 173.27, 165.49, 164.49, 140.57, 136.86, 136.30 (d, *J* = 56.2 Hz), 134.69 (d, *J* = 58.2 Hz), 131.22, 131.06, 130.57, 129.74, 129.01, 128.96 (d, *J* = 10.3 Hz), 128.60 (d, *J* = 10.1 Hz), 128.11, 128.02, 113.40, 112.22, 111.37, 110.06, 109.99, 109.48, 100.03, 88.51, 87.95, 87.71, 87.27, 87.07, 75.67, 74.90, 72.27, 71.30, 65.47, 61.32, 59.62, 55.39, 54.75, 52.55, 49.27, 45.74, 44.73, 41.04, 40.93, 38.85, 34.64, 33.89, 32.45, 32.32, 31.95, 31.88, 31.18, 27.12, 26.41, 26.09, 23.44, 21.96, 20.85, 19.18, 19.11, 18.37, 17.64, 15.81, 15.28, 14.95, 14.02, 12.94; HRMS (ESI-TOF) *m/z* calcd for $C_{75}H_{101}CoN_{13}O_{15}P_2Na$ $[M+Na+]^{2+}$ 783.8117 found 783.8114; UV/vis (MeOH) λmax (nm) (ε, M^{-1} cm^{-1}): 266 (2.4×104), 325 (1.9×104), 431 (1.2×104); HPLC: $t_{analytical\ 1}$ = 15.32 min, $t_{preparative}$ = 16.2 min.

Compound (CN)4

Compound **(CN)4** was synthesized according to the general procedure described for CDT coupling yielding 17 mg (46%, 13 µmol) of red solid.

^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 5.80 (s, 1H), 4.28 (t, *J* = 7.1 Hz, 2H), 4.10 (d, *J* = 8.7 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.58 – 3.55 (m, 1H), 3.46 – 3.40 (m, 1H), 3.35 (s, *J* = 8.0 Hz, 1H), 3.16 (ddd, *J* = 27.3, 13.9, 7.2 Hz, 4H), 3.09 (s, 1H), 2.96 (s, 1H), 2.59 (s, 3H), 2.52 (d, *J* = 13.9 Hz, 1H), 2.46 (d, *J* = 9.4 Hz), 2.40 (s, 3H), 2.37 (s, 3H), 2.27 (d, *J* = 6.6 Hz, 7H), 2.22 – 2.14 (m, 2H), 2.14 – 2.00 (m, 5H), 2.00 – 1.78 (m, 3H), 1.70 (s, *J* = 5.0 Hz, 3H), 1.46 (s, 3H), 1.41 (s, 2H), 1.31 (dd, *J* = 13.9, 7.1 Hz, 2H), 1.24 (s, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 2H), 1.17 (d, *J* = 1.9 Hz, 2H), 1.16 (s, 3H), 1.15 (s, 4H), 0.90 (t, *J* = 7.1 Hz, 2H); HRMS (ESI-TOF) *m/z* calcd for $C_{62}H_{87}CoN_{15}O_9$ $[M]^+$ 1244.6143 found 1244.6135; UV/vis (MeOH) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 279 (1.7×104), 361 (2.6×104), 519 (8.4×103), 540 (8.4×104); HPLC: $t_{analytical\ 2}$ = 7.47 min, $t_{preparative}$ = 12.86 min.

Compound (CN)5

Compound **(CN)5** was synthesized according to the general procedure described for CDT coupling yielding 6.5 mg (18%, 4.9 µmol) of red solid.

^{1}H NMR (500 MHz, CD_3OD) δ 7.28 (dd, *J* = 14.7, 7.2 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.81 (s, 1H), 4.27 (q, 2H), 4.12 (d, *J* = 9.0 Hz, 1H), 3.79 (d,*J* = 10.7 Hz, 1H), 3.76 (s, 2H), 3.56 (d, *J* = 4.7 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.1 Hz, 1H), 3.24 (dd, *J* = 13.9, 7.3 Hz, 1H), 3.15 (s, 1H), 3.01 – 2.93 (m, 1H), 2.63 (dd, *J* = 14.0, 9.7 Hz, 2H), 2.59 – 2.55 (m, 1H), 2.52 (d, *J* = 13.8 Hz, 2H), 2.48 (dd, *J* = 10.6, 4.8 Hz, 1H), 2.38 (ddd, *J* = 24.8, 14.0, 8.4 Hz, 3H), 2.30 (s, *J* = 7.4 Hz, 3H), 2.28 (s, 3H), 2.26 – 2.14 (m, 2H), 2.12 (d, *J* = 9.2 Hz, 1H), 2.10 (s, 1H), 2.08 – 1.88 (m, 3H), 1.88 – 1.79 (m, 2H), 1.70 (s, 3H), 1.51 (t, *J* = 6.6 Hz, 4H), 1.42 (s, 3H), 1.35 – 1.28 (m, 2H), 1.25 (d, *J* = 12.5 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.19 (s, 3H), 1.17 (d, *J* = 7.0 Hz, 2H), 1.15 (d, *J* = 6.2 Hz, 1H), 0.90 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 176.88, 176.81, 176.71, 176.19, 174.41, 174.30, 173.54, 172.36, 163.42, 163.01, 157.22, 142.58, 139.39, 128.31, 126.03, 125.80, 125.48, 104.74, 102.74, 90.69, 83.15, 75.10, 69.81, 65.46, 58.68, 56.89, 56.35, 55.24, 53.55, 49.08, 46.41, 46.04, 45.25, 44.07, 43.60, 43.35, 41.30, 38.76, 34.83, 33.89, 32.79, 32.08, 31.54, 31.27, 31.17, 30.37, 27.00, 25.26, 21.96, 21.47, 18.43, 17.99, 16.93, 16.84, 15.91, 14.73, 14.51, 14.01, 12.93; HRMS (ESI-TOF) *m/z* calcd for $C_{58}H_{82}CoN_{14}O_9$ $[M]^+$ 1177.5721 found 1177.5712; UV/vis (MeOH) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 277 (1.7×104), 354 (2.6×104), 495 (8.4×103), 523 (8.4×104); HPLC: $t_{analytical\ 2}$ = 6.00 min, $t_{preparative}$ = 10.23 min.

Compound (CN)6

Compound **(CN)6** was synthesized according to the general procedure described for CDT coupling yielding 16 mg (43%, 12 µmol) of red solid.

^{1}H NMR (500 MHz, CD_3OD) δ 7.32 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 2.8 Hz, 1H), 7.08 (t, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.57 (t, *J* = 5.7 Hz, 1H), 5.78 (s, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.56 (dd, *J* = 14.6, 6.4 Hz, 1H), 4.50 (d, *J* = 14.9 Hz, 1H), 4.12 (d, *J* = 8.7 Hz, 1H), 3.77 (d, *J* = 10.6 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.42 (dd, *J* = 14.0, 3.2 Hz, 1H), 3.34 (s, 1H), 3.17 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.93 (dd, *J* = 10.4, 5.8 Hz, 1H), 2.87 (s, 1H), 2.60 (d, *J* = 4.5 Hz, 2H), 2.56 (d, *J* = 12.9 Hz, 1H), 2.51 (d, *J* = 13.6 Hz, 3H), 2.46 (d, *J* = 4.8 Hz, 1H), 2.42 – 2.37 (m, 1H), 2.36 (s, 1H), 2.27 (s, *J* = 11.1 Hz, 2H), 2.24 – 2.13 (m, 3H), 2.11 (s, 3H), 2.10 – 2.04 (m, *J* = 11.0, 6.5 Hz, 2H), 2.01 – 1.91 (m, 3H), 1.86 – 1.77 (m, 2H), 1.69 (s, *J* = 17.3 Hz, 3H), 1.48 (s, 3H), 1.46 (s, 2H), 1.41 (dd, *J* = 19.5, 8.5 Hz, 2H), 1.36 (s, 2H), 1.29 (dd, *J* = 18.9, 9.5 Hz, 2H), 1.26 – 1.20 (m, 3H), 1.19 (s, 1H), 1.17 (s, 2H), 1.16 (s, 3H), 0.90 (t, *J* = 6.8 Hz, H); ^{13}C NMR (126 MHz, CD_3OD) δ 178.41, 178.32, 178.23, 178.15, 178.11, 177.64, 175.84, 175.69, 174.97, 173.69, 164.80, 164.36, 158.64, 137.72, 131.27, 127.96, 125.63, 122.27, 119.02, 111.73, 106.12, 104.17, 100.61, 92.06, 84.55, 76.43, 71.25, 66.89, 60.06, 57.73, 56.64, 54.82, 50.51, 47.74, 47.46, 45.11, 44.77, 44.05, 42.71, 40.07, 36.25, 34.25, 33.42, 32.97, 32.74, 32.48, 31.83, 28.41, 26.66, 26.44, 23.69, 22.85, 19.85, 19.41, 18.35, 18.27, 17.32, 16.15, 15.83, 15.43, 14.41; HRMS (ESI-TOF) *m/z* calcd for $C_{59}H_{80}CoN_{14}O_9$ [M]+ 1187.5565 found 1187.5555; UV/vis (MeOH) λ_{max} (nm) (ε, M^{-1} cm^{-1}): 277 (1.7×104), 354, (2.6×104), 495 (8.4×103), 523 (8.4×104); HPLC: $t_{analytical\ 2}$ = 6.82 min, $t_{preparative}$ = 11.04 min.

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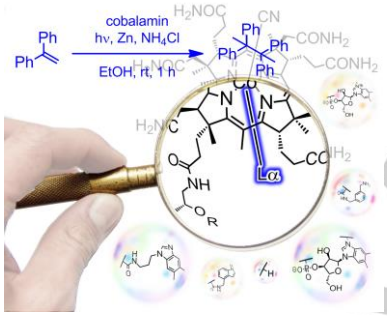

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